REMARKS

A. Rejection of Claims 1-40 Pursuant to 35 U.S.C. §112, First Paragraph:

Claims 1-40 stand rejected pursuant to 35 U.S.C. §112, first paragraph as non-enabled by the teaching of the specification. The examiner asserts two basic grounds of rejection:

(1) that the claims are overly broad in that they encompass subject matter which one of skill in the art would be unable to construct based on the teaching of the specification;

and

(2) that the claimed subject matter relates to methods of gene therapy and compositions for use in gene therapy, and given the alleged unpredictability of the art of gene therapy, the specification fails to provide one of skill in the art with sufficient guidance to make and use the invention as claimed.

Applicants traverse.

Similar to the positions taken in the first Office Action relating to this application dated January 21, 2000, the rejection of the pending claims pursuant to 35 U.S.C. §112, first paragraph the alleged "unpredictability" of "gene therapy" remains at the core of the Examiner's rejections of the pending claims. Applicants believed that they addressed the grounds of rejection reiterated by the examiner in the present Office Action in their previous Response of July 21, 2000 and would reincorporate those comments at the present time. Applicants believe that the essence of the disagreement underlying all grounds of rejection pursuant to 35 U.S.C. §112, first paragraph presented by the Examiner in the Office Action arise from a primary core issue: that the standard of review being applied to this application is improper. Therefore, the Applicants would take this opportunity to discuss the bases of rejection of the pending claims and to present evidence that the Examiner is applying an inappropriate standard of review to this application.

In the present Office Action examiner cites the Dang, et al and Eck and Wilson publications, alleging

> None of these unpredictable factors discussed by Dang and Eck were specially addressed in applicant's disclosure. The instant specification does not teach the site of delivery, composition and quantities of the adenoviral vector used to be able to measure the effects of administration of any viral vector except by prophetic consideration. Further, it is unclear that from the cell culture example

> which indicates the multiplying capacity of the defective adenovirus in normal cells versus tumor cells having defective p53 and Rb pathways, where the p53 and Rb pathways are restored in the tumor cells due to the multiplying capacity of the adenoviral vector, that one could support the broad claims directed to any viral vector administered in vivo or ex vivo in view of the predictability of the art.

First, Applicants believe that the Examiner's understanding of the present invention is flawed. The vectors of the present invention do not "restore the p53 or Rb pathways" and are at a loss to comprehend how the "multiplying capacity of the adenoviral vector" could possibly restore the p53 or Rb pathways. The vectors of the present invention selectively replicate in tumor cells in which the p53 or Rb pathways (for example) are defective, but they do not attempt to restore these pathways by introduction of functional Rb or p53 sequences. The vectors are designed to "sense" presence of such defective pathways and selectively kill such cells by replication and lysis.

Regarding the Dang reference, Applicants would like to initially note that this reference is merely the report of attendees at a Conference held in LaJolla California on March 4-5 1998. It presents no scientific data or results, but is merely the impression of attendees on the state of gene therapy as presented at this meeting. Secondly, the passage of this reference cited by the examiner in support of the notion that gene therapy is unpredictable is merely the authors' characterization of the nearly six year old Orkin and Motulsky report entitled "Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy" dated December 7, 1995. The purpose of the evaluation summarized in this report was characterized in the first paragraph of the report which states "The Panel was asked specifically to comment on how funds and efforts should be distributed among various research areas and what funding mechanisms would be most effective in meeting research goals." Although this report did indicate that gene therapy does have challenges which need to be overcome, it did recommend the funding of research toward these goals as legitimate research efforts. It did not dismiss gene therapy as a pipe dream. Indeed, it analogized gene therapy to other therapies once considered fanciful stating,

> Typically, many years are required before new therapies are proved successful. For example, transplantation of bone marrow and other organs--now an accepted therapy for life-threatening diseases-required more than two decades of development during which frequent failures often provoked widespread skepticism.

Consequently, Applicants believe that the Dang et al reference and the Orkin and Motulsky report merely highlight challenges that need to be overcome in any new treatment modality. Indeed, much of what is said about gene therapy in the Report merely restates many of the challenges inherent in drug discovery generally. According to the Pharmaceutical Manufacturers Association, of every 5000 compounds evaluated, on average, only 5 enter clinical trials and only 1 of those is approved for patient use. However, this "failure rate" if you will is not a bar to the patentability of traditional pharmacological agents. The MPEP specifically states:

> Recently, the Federal Circuit reiterated that therapeutic utility sufficient under the patent laws is not to be confused with the requirements of the FDA with regard to safety and efficacy of drugs to marketed in the United States.
>
> > FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. Scott [v. Finney], 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 [(Fed.Cir. 1994)]. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.
>
> In re Brana, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995). Accordingly, Office personnel should not construe 35 U.S.C. 101, under the logic of "practical" utility or otherwise, to require that an applicant demonstrate that a therapeutic agent based on a claimed invention is a safe or fully effective drug for humans. See, e.g., In re Sichert, 566 F.2d 1154, 196 USPQ 209 (CCPA 1977); In re Hartop, 311 F.2d 249, 135 USPQ 419 (CCPA 1962); In re Anthony, 414 F.2d 1383, 162 USPQ 594 (CCPA 1969); In re Watson, 517 F.2d 465, 186 USPQ 11 (CCPA 1975).

Similarly, the fact that the specification does not present *in vivo* data does not preclude a finding of patentability of the claimed subject matter. In the same section of the MPEP cited above, it states:

> Similarly, courts have found utility for therapeutic inventions despite the fact that an applicant is at a very early stage in the development of a pharmaceutical product or therapeutic regimen based on a claimed pharmacological or bioactive compound or composition. The Federal Circuit, in Cross v. Iizuka, 753 F.2d 1040,

1051, 224 USPQ 739, 747-48 (Fed. Cir. 1985), commented on the significance of data from in vitro testing that showed pharmacological activity:

> We perceive no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, in vitro testing, may establish a practical utility for the compound in question. Successful in vitro testing will marshal resources and direct the expenditure of effort to further in vivo testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an in vivo utility.

Applicants believe that the Examiner is applying an improper standard to evaluate the patentability of the claimed invention merely by referring to it as "gene therapy."

In the present Office Action, the Examiner remains of the position that the present specification fails to provide sufficiently specific guidance relating to the administration of the vectors of the present invention such that one of skill in the art would be able to practice the present invention in a clinically useful manner. In the previous Response, the Applicants discussed at length the issues surrounding the therapeutic application of the present vectors. Applicants believes that the comments previously of record address this point clearly. Applicant further believes that the Examiner is applying a standard which is not in keeping with the standard applied to other patent applications relating to gene therapy in this regard. For example, Applicant would bring to the Examiner's attention Cuthbertson, United States Patent No. 6,204,251 issued March 20, 2001 based on a priority specification filed October 31, 1994. Claim 1 of this issued patent reads:

> 1. A method of treating ocular disease comprising incorporating exogenous nucleic acid into an in situ ocular cell under conditions permissive for the uptake of said exogenous nucleic acid, said exogenous nucleic acid encoding a protein associated with said ocular disease, whereby said exogenous nucleic acid is expressed and said disease is treated.

This claim is not restricted to a particular disease state, protein to be expressed, method of administration or type of vector. In the Office Action the Examiner takes the position that the present specification is deficient in that it fails to provide any guidance as to the level of gene expression required, the number of transduced cells needed, the route and time course of administration, the site of administration, etc. When comparing the claims of Cuthbertson in

view of the specification, it is clear that the Office required very little guidance relating to dosing, frequency of administration, etc.

The Office's position is reflected in the scope of the claims other issued United States Patents relating to gene therapy are not limited in scope regarding particular routes of administration or to narrow disease states. The following is a summary of claims of issued United States patents to illustrate this point: United States Patent No. 6174871 entitled "Gene therapies for enhancing cardiac function" provides as claim 1:

> 1. A method for treating **a heart disease**, wherein said heart disease includes a symptom of myocardial ischemia, by increasing blood flow to the myocardium of a patient, comprising delivering a replication-deficient adenovirus vector to the myocardium by intracoronary injection directly into the lumen of one or more coronary arteries, said vector comprising a gene the expression of which causes production of an angiogenic protein or peptide, thereby increasing blood flow to the myocardium.

and claim 20 of the same patent provides:

> 20. A method for treating a heart disease, wherein said heart disease includes a symptom of myocardial ischemia, by increasing the contractile function of the myocardium of a patient, comprising delivering a replication-deficient adenovirus vector to the myocardium by intracoronary injection directly into the lumen of one or more coronary arteries, said vector comprising a gene the expression of which causes production of an angiogenic protein or peptide, thereby increasing the contractile function of the myocardium.

United States Patent No. 5871726 entitled "Tissue specific and tumor growth suppression by adenovirus comprising prostate specific antigen" provides claims to a vector claim 1:

> 1. An adenovirus vector comprising an adenovirus gene essential for propagation under transcriptional control of a prostate specific response element, said prostate cell specific response element comprising an enhancer specific for prostate specific antigen and a promoter.

and an *in vivo* method of use of such vector in claim 30:

> 30. A method for suppressing tumor growth comprising introducing the adenovirus vector of claim 1 into a tumor cell expressing prostate specific antigen (PSA), wherein introduction of the adenovirus vector results in suppression of tumor growth.

United States Patent No. 6197293 entitled "Adenovirus vectors specific for cells expressing androgen receptor and methods of use thereof"

1. A replication-competent adenovirus vector comprising an adenovirus gene under transcriptional control of a probasin transcriptional regulatory element (PB-TRE).

14. The adenovirus vector of claim 1, further comprising at least one additional adenovirus gene under transcriptional control of at least one additional prostate-specific transcriptional regulatory element.

20. A method of suppressing tumor cell growth, said method comprising contacting a tumor cell with an adenovirus vector of claim 1 such that the adenovirus vector enters the tumor cell and exhibits selective cytotoxicity for the tumor cell.

32. A method of suppressing tumor cell growth, said method comprising contacting a tumor cell with an adenovirus vector of claim 14 such that the adenovirus vector enters the tumor cell and exhibits selective cytotoxicity for the tumor cell.

United States Patent No. 6096303 entitled "Method to enhance treatment of cystic tumors" provides as claim 1:

1. A method for delivery of genetic material or the product thereof to the cells of a cystic tumor comprising

- injecting the genetic material into the tumor cyst fluid within the cystic tumor,
- wherein the genetic material or product expressed from the genetic material is present in the tumor cyst fluid in an amount effective to kill cystic tumor cells.

United States Patent No. 6066624 entitled "Gene therapy for solid tumors using adenoviral vectors comprising suicide genes and cytokine genes" provides as claim 1:

1. A method of causing regression of a solid tumor in a mammal, comprising the steps of:

- administering an adenoviral vector directly into said tumor, wherein said vector is comprised of a DNA sequence encoding a suicide gene, and one or more cytokine genes, wherein said genes are operably linked to a promoter, and wherein said tumor expresses said suicide gene and said one or more cytokine genes; and
- administering a prodrug in amounts sufficient to cause regression of said tumor when said prodrug is converted to a toxic compound by said suicide gene.

United States Patent No. 6,096,718 entitled "Tissue specific adenovirus vectors for breast cancer treatment" provides as claim 1:

1. A method for killing breast cancer cells in a tumor in a mammal, comprising:

- a. delivering to the tumor a replication incompetent adenovirus vector having deletions in the adenoviral E1 and E3 genes, said adenovirus vector comprising a human .alpha.-lactalbumin promoter operatively linked to the HSV-TK gene, whereby the HSV-TK gene is expressed, and

- b. administering to the mammal an effective amount of a gancyclovir, whereby the breast cancer cells are killed.

United States Patent No. 6,100,242 entitled "Gene therapies for enhancing cardiac function" provides as claim 1:

> 1. A method for increasing contractile function in the heart of a patient, comprising delivering a transgene encoding an angiogenic protein or peptide to the myocardium of the patient by introducing a replication-deficient adenovirus vector comprising the transgene into the lumen of a coronary artery supplying blood to the myocardium, whereby the transgene is delivered to the myocardium and expressed and contractile function in the heart is increased.

United States Patent No. 6,001,816 entitled "Gene therapy for leptin deficiency" provides as claim 1:

> 1. A method of treating obesity in a mammal having a deficiency in functional leptin comprising administering intravenously to the mammal an adenoviral vector comprising a DNA sequence encoding a leptin operably linked to a promoter and expressing the DNA sequence, wherein the mammal exhibits a decrease in body weight, a decrease in serum glucose levels and/or a decrease in serum insulin levels.

United States Patent No. 5830458 entitled "Method for destroying a diseased human cell" provides as claim 1:

1. A method for destroying a diseased human cell, said method comprising:
- a) infecting a human cell with a replication defective recombinant retrovirus comprising a recombinant gene operatively linked to a promoter, said gene encoding a protein which converts a purine-based or pyrimidine-based drug to a second compound that is toxic to said infected human cell;
- b) administering said purine-based or pyrimidine-based drug to said infected human cell when said cell is in a diseased state, said diseased state being a viral infection, a cancer, or graft versus host disease, said purine-based or pyrimidine-based drug reacting with said protein to form a therapeutic agent that is toxic to said diseased cell in an amount that is lethal to said cell, whereby said diseased cell is destroyed.

None of these claims is limited to specific disease state and a particular mode of administration and a particular level of expression of the therapeutic gene and any particular vector and any targeting method in the manner suggested as necessary by the Examiner in this instance. In view

of the foregoing, Applicant believes that the standard being applied by the Examiner in this instance is unduly restrictive and improper.

Furthermore, as indicated in the first Response in this application, the Applicants questioned whether or not the present invention would even fall within the scope of what might be termed by some as "gene therapy." Applicant would direct the Examiner's attention to the file history of the McCormick, United States Patent Application Serial No. 08/484,938, now United States Patent No. 5,801,029 issued September 1, 1998. In this application, the USPTO took the position that the recombinant adenoviral vectors described and claimed in that application should be considered gene therapy. The office action issued January 29, 1997 in that application states:

> The claims are direct to methods of ablating neoplastic cells in a population which encompasses gene therapy methods. However the specification fails to adequately teach how to use the viral constructs of the present invention for in vivo gene therapy. Gene therapy s a highly unpredictable and undeveloped field and the skill in the art is high.

In the applicant's response filed June 26, 1997, McCormick took the position that the invention did not encompass "gene therapy" stating:

> Support for Applicant's view that the invention is not gene therapy is provided in the form of a declaration under 35 U.S.C. 1.132 by Dr. Chris Maack, Onyx's Director of Regulatory Affairs and Clinical Operations. Dr. Maack declares that he sought guidance regarding the status of an Onyx virus representative of those described in Applicant's specification from the Office of Recombinant DNA Activity of the National Institutes of Health prior to starting clinical trials. Specifically, he inquired whether the use of the virus would be considered gene therapy. If so, Onyx would have been required to get Recombinant DNA Advisory Committee (RAC) approval, or if not, Onyx wold only have needed FDA approval.

A copy of the response and the Maack declaration and its associated exhibits is attached to this Response as Exhibit A. As can be seen from the declaration and the associated correspondence, the RAC did not consider the use of a therapeutic virus to be gene therapy subject to their jurisdiction. Following the presentation of this evidence to the patent office, the "gene therapy is unpredictable" rejection was withdrawn. As the therapeutic vectors of the present invention are designed to selectively replicate in and lyse neoplastic cells (although the effect may be enhanced by other factors) there is reason to believe that the methodology and vectors of the

present invention would be considered similarly and believe that applying the "gene therapy" label to the present invention is subject to question.

Therefore, the Applicants believe that in regard to the present invention, the Examiner is applying an inappropriate standard of review based on the label of "gene therapy," which is questionably applicable to the present invention. Applicants do not believe that there is any sound reason to view the present invention differently than any other pharmacological agent. The clinical experience and success rate of gene therapy agents is not significantly different than the experience with other conventional "small molecule" agents -- therefore the same standard should apply. Secondly, if the Examiner is going to categorize this invention as "gene therapy," the review of this application should be consistent with the standard of review applied in other gene therapy cases. Applicants believe that the foregoing demonstrates that the standard being applied by the Examiner in rejecting the pending claims 1-40 pursuant to 35 U.S.C. §112, first paragraph is improper and respectfully request that this ground of rejection be withdrawn.

B. Rejection of Claim 35 Pursuant to 35 U.S.C. §102(e):

Claim 35 is rejected pursuant to 35 U.S.C. §102(e) as anticipated by Buckbinder, *et al.* Claim 35 is directed to two specific promoter sequences described in the specification, p53CON and RGC. Although Buckbinder, *et al.* may teach certain sequences common to such p53 pathway responsive promoters, it does not teach these promoters specifically. In order to constitute an anticipatory reference, the reference must describe every element of the claimed invention. The Buckbinder, *et al.* reference fails to meet this standard and is not proper 102 reference. Consequently, Applicants submit that the rejection of Claim 35 pursuant to 35 U.S.C. §102(e) improper and respectfully request that it be withdrawn.

C. Rejection of Claim 36 Pursuant to 35 U.S.C. §102(e):

Claim 36 is rejected pursuant to 35 U.S.C. §102(e) as anticipated by Grainger, *et al.* Claim 36 is directed to two specific promoter sequences described in the specification, PAI and SRE. Although Grainger, *et al.* may that reduced TGF-beta levels might be due to various

factors one which is the presence of the 4G allele of the PAI-1 promoter responsive promoters, it does not teach these promoters specifically. In order to constitute an anticipatory reference, the reference must describe every element of the claimed invention. The Grainger, *et al.* reference fails to meet this standard and is not proper §102 reference. Consequently, Applicants submit that the rejection of Claim 36 pursuant to 35 U.S.C. §102(e) improper and respectfully request that it be withdrawn.

CONCLUSION

Applicants believes that all grounds of rejection set forth in the office action of November 13, 2000 have been traversed for the foregoing reasons of fact and law. Applicant therefore respectfully requests that all grounds of rejection of the pending claims be withdrawn and this case passed to issuance without delay.

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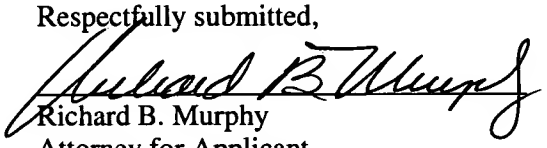
Respectfully submitted,



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